PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

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PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB2005/050003	06.01.2005	08.01.2004

International Patent Classification (IPC) or both national classification and IPC
C07D491/04, A61K31/407

Applicant
MEDIVIR UK Ltd

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/GB2005/050003

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-30
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-30
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-30
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (SEPARATE SHEET)

Re Item V

1. Cited prior art

D1: WO 02057270 (cited in the application)
D2: WO 02088106 (cited in the application)
D3: WO 9850533

2. Novelty

The novelty lies in the necessary presence of at least one halogen atom (R1 and/or R2) on the condensed furo-pyrrole system. The closest prior art compounds are disclosed in D1 and differ essentially by the absence of at least one halogen atom on the position 6 of the furo-pyrrole group.

3. Inventive step

3.1 According to the description, the problem underlying the present application is to provide cystein protease inhibitors useful in the prevention or treatment of disorders related to cathepsin K.

The cited prior art documents relate to the same problem.

3.2 This difference appears to be structurally a very minor modification of the closest prior art, especially in view of all the other larger variants claimed. Nevertheless the Applicant has provided a comparison test between two compounds which only differ in the presence of a fluorine atom: reference compound is example 10 of D1 compared to example 6 of the invention. The result shows that the difference leads to an significant increase on potency measured by cathepsin K K^i (nM). This can serve the acknowledgment of the presence of an inventive step if it can be established convincingly that this is representative over the whole claimed scope.

3.3 Further remarks

The Applicant's attention is drawn to the fact that the claims as presently drafted may not fully satisfy PCT requirements. Particularly, the protection which is sought should comply with a reasonable breadth of a scope covering only variants and/or compounds which solve the problem underlying the invention.

It is realized that the Applicant is entitled to claim all **obvious** modifications of what was concretely described and that alternative variations have to be supported by the description, *i.e.* a certain number of examples.

The claims, especially claim 1, cover a very large amount of variants and extend the claimed scope beyond what has actually been verified by worked examples wherein constant features are E = C=O (except one case: OC=O); R3 = isobutyl and R4 = H (except one case wherein R3 and R4 form together a cyclohexyl) and the given stereoconfiguration of the fluoro-6-furo(3,2-b)pyrrol system.

Excessively broad meanings (*e.g.*, monocyclic/bicyclic carbocycle/heterocycle) render the claims **obscure in scope** and do not allow to correctly and specifically circumscribe a scope where the invention applies and for which protection can actually be granted (see also PCT Guidelines C-III, 4.1-4.4, Rule 6.3 PCT, technical features).

The question is whether or not a technical effect is to be achieved by all the embodiments covered by the claims when this technical effect turns out to be the sole reason for the alleged inventiveness of these processes. A consequence is that broad expressions are objectionable under Art. 33(3) PCT.

The given examples represent a very narrow illustration of the claimed scope. It can be therefore questioned whether the regularly occuring groups in the examples is a necessary and essential characterisitic of the invention which should not be allowed to vary out of the ***reasonable*** extent of the usual equivalents and (bio)isosters of these variants, especially keeping in mind that the difference with the prior art is relatively small, the effect (to be unexpected) of which can be hindered by other unpredicted effects of larger structural variations of other variant groups. Without any evidence of the contrary, the presently claimed scope may not represent a reasonable generalization of the very invention as

shown by the examples.

Open and too broad formulations may also lead to unacceptable **speculations** from the skilled people as to the very invention and its future aspects; it may even suggest that the claimed scope lacks any inventive merit and is not properly covered by the description and, particularly, the examples. Furthermore this would deprive any third party from a legitimate protection for a genuine invention in relation with an object which was neither described nor even foreseen but would have only been a hypothesis in the frame of the present invention.

There is indeed a great variety of structural possibilities which are claimed (and not yet explored by the Applicant), the *effect of which cannot be foreseen* having regard to the problem underlying the present application and, consequently, which are not solutions of the problem.

The inventive step required by the PCT can be acknowledged only for a well-defined scope embracing a specific domain thanks to a reasonable generalisation of the very invention, taking into account the extent of the illustration of the examples, the support of the specification, the closeness of the prior art, the reproducibility and the feasability of the invention. In other words, the protection which is sought should comply with a reasonably broad claimed scope such that it comprises only compounds, their variants and equivalents which solve the problem underlying the invention.

4. Miscellaneous

4.1 The insertion of a sentence like the last paragraph of page 103 ("...but not to the exclusion... etc") which may also refer to an extent of protection beyond the actual invention is objectionable because it would suggest that the subject-matter as presently disclosed does not cover properly the claimed scope. Any expression which can be interpreted as an unjustified extension of the claimed scope should be objected. The specification should be clear and sufficient by itself. A precautionary measure on the limits of the scope is therefore superfluous and even misleading as it finally prevents a proper definition of the invention and opens the way to speculations (of skilled persons) about the

very inventive subject-matter. Consequently any element against clarity has to be deleted/has been cancelled.

4.2 It is additionally noted that the terms and/or expressions like "etc", "and the like" used in these definitions are unspecific. They cannot serve as a support for the invention and therefore should be deleted.

Re Item VIII

There are major unclarities and inconsistencies, particularly in the definition of R6, throughout the whole application.

1. X is a chain link and therefore must be defined as a *bivalent* group when it is not a bond: alkyl is a monovalent group and thus not a correct definition. It should be named "alkylenyl"; additionally the indication of the link position (a hyphen) should be clearly marked near X.

2. R6 is said to be optionally substitued by R7 which can be substituted by a rest R9 (*i.e.* -X-R9 wherein X is a bond) which itself can be substituted by R10 which in turn can be substitued by rests comprising R9 groups. This creates a endless repeating situation which is not admissible. At least the last groups R9 must be renamed, like, for instance, R9', in order to set clearly the endgroups.

3. In the definition of R7, the groups -X-O-R9 and -O-X-R9 unnecessarily overlap; a more concise definition should be given.

4. Furthermore, said "*further representative R6 groups*" recited at the bottom of page 8 are not comprised in the claim 1 definitions because the end group -NRqRq' does not illustrate the claimed compounds: in the structurally closest claimed group -XNRbR9, R9 covers the definition of Rq but Rb cannot represent an alkanoyl; moreover, Rb and R9 cannot form together a ring.

5. The same remark applies to three of the said "*currently preferred R6 groups*" of page 9: the one wherein the *methoxyethyl*-piperazine group (*i.e.*, R9 = piperazinyl but R10 cannot represent a methoxyethoxy final rest): the other ones with *fluorine* substituent (halogen is not a possible value for R10).

6. Compounds of page 11 ("building blocks P1) said "*further aspect of the invention*" are not claimed and consequently are not part of the invention. The same remark applies to "building blocks P3" of page 12.

7. It is understood that the Applicant does not wish to be bound to any theory (pages 3, and 18) but, for reason of consistency and coherence, if the present compounds of formula II can be described as a P1-P2-P3 system, when P1 and P2 appear relatively well defined, the same clear principle should be apply to P3 which, consequently, considering formula II, represents the left end portion R6-E-. The P3 segment shown on Table C, page 12-15, are therefore not consistent when the chain link E is absent (it is never defined to be possibly a bond). The two P3 groups with fluorine atoms already mentioned above (No. 5) are repeated on page 14 but they cannot illustrate the invention as claimed. The two P3 groups with a methoxyethyl end group on page 15 cannot be also illustrative of the invention as claimed.

8. The definitions in claim 25 -OR9/-OXR9 and -NRbR9/-NRbXR9 are redundant since, by reference to claim 1, X is defined as possibly being a bond. For clarity reason, this repetition should be avoided.

9. The invention cannot be extend to "*prodrugs, complexes and other forms*" which have not been clearly and specifically defined (page 16).

10. For reason of consistency, it should be avoided to use the same symbol for different meanings along the application: see R3 in claim 1 and on page 18.
The formula I mentioned on page 18 is believed to refer to the structure taken from prior art D1 cited on page 1.

11. Note that the designation of "example" to the partial synthesis on pages 41-44 ("examples" 1-3) is misleading since they are not actual illustrations of the claimed

compounds. "Examples" 8.1 (ring R6 is absent), 8.14 (R6 cannot represent a benzyl rest - E taken as OC=O), 8.17 (see above), 8.18 (R10 cannot be -CF3), 8.21 (see above), 8.28 to 8.30 (the vinylenyl chain link is not claimed), 8.42 and 8.43 (R10 cannot be halogen), 8.52 (see above) do not illustrate the invention as well.